Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	336	venom near4 (protease$1 or metalloproteinase$1 or metalloprotease$1)	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:04
L2	1993	cobra	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:04
L3	22	1 same 2	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:05
L4	1265	psgl or (p adj selectin)	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:05
L5	118	(protease$1 or metalloproteinase$1 or metalloprotease$1) same 4	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:05
L6	14	1 and 5	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:06
L7	9	mocarhagin	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:06
L8	34	3 or 6 or 7	US-PGPUB; USPAT	OR	OFF	2004/06/16 10:06

2/18/98

PGPUB-DOCUMENT-NUMBER: 20040087539

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040087539 A1

TITLE: Method of treating conditions related to platelet activity

PUBLICATION-DATE: May 6, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Du, Xiaoping	Westmont	IL	US	

APPL-NO: 10/ 467387

DATE FILED: December 12, 2003

PCT-DATA:
APPL-NO: PCT/US02/03372
DATE-FILED: Feb 5, 2002
PUB-NO:
PUB-DATE:
371-DATE:
102(E)-DATE:

US-CL-CURRENT: 514/45, 514/263.3

ABSTRACT:

Methods of treating thrombotic and hemostatic conditions related to platelet activity are described herein. The methods of treating thrombotic and hemostatic conditions use active agents that modulate production of guanosine 3', 5' cyclic monophosphate (cGMP) or the function of cGMP-dependent protein kinase (PKG), and its downstream effectors, the ERK and p38 pathways.

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Patent Application No. 60/267,326, filed Feb. 8, 2001.

---------- KWIC ---------

Detail Description Paragraph - DETX (147):
[0168] 17. Ward C M, Andrews R K, Smith A L, Berndt M C; Mocarhagin, a novel cobra venom metalloproteinase, cleaves the platelet von Willebrand factor receptor glycoprotein Lbalpha. Identification of the sulfated tyrosine/anionic sequence Tyr-276-Glu-282 of glycoprotein Ibalpha as a binding site for von Willebrand factor and alpha-thrombin. Biochemistry 35:4929-4938, 1996

PGPUB-DOCUMENT-NUMBER: 20040002450

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040002450 A1

TITLE: Y17 - isolated molecules comprising epitopes containing sulfated moieties, antibodies to such epitopes, and uses thereof

PUBLICATION-DATE: January 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lazarovits, Janette	Reut		IL	
Hagay, Yocheved	Rehovot		IL	
Plaksin, Daniel	Rehovot		IL	
Vogel, Tikva	Rehovot		IL	
Nimrod, Abraham	Rehovot		IL	
Mar-Ham, Hagit	Aseret		IL	
Szanthon, Ester	Rehovot		IL	
Richter, Tamar	Nes Tziona		IL	
Amit, Boaz	Kiron		IL	
Cooperman, Lena	Rishon Lezion		IL	
Peretz, Tuvia	Hod Hasharon		IL	
Levanon, Avigdor	Rehovot		IL	

APPL-NO: 10/ 032423

DATE FILED: December 31, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60258948 20001229 US

US-CL-CURRENT: 514/12, 514/13 , 514/14 , 514/15 , 514/16 , 530/324 , 530/325 , 530/326 , 530/327 , 530/328

ABSTRACT:

The present invention provides epitopes present on cancer cells and important in physiological phenomena such as cell rolling, metastasis, and inflammation. Therapeutic and diagnostic methods and compositions using antibodies capable of binding to the epitopes are provided. Methods and compositions according to the present invention can be used in diagnosis of and therapy for such diseases as cancer, including tumor growth and metastasis, leukemia, auto-immune disease, and inflammatory disease

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a Continuation-in-Part application of U.S. provisional application Serial No. 60/258,948, filed on Dec. 29, 2000, the subject matter of which is incorporated by reference hereto.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX

(8):
[0187] FIG. 7 depicts a Western blot demonstrating that Y1 binds the N-terminal (His 1-Glu 282) fragment of platelet GPIb.alpha. after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX
(9):
[0188] FIG. 8 depicts a Western blot showing binding of Y1 and Y17 to glycocalicin after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX
(14):
[0193] FIG. 13 depicts a Western blot demonstrating that cleavage of glycocalicin by mocarhagin and cathepsin G abolishes binding of Y1.

Brief Description of Drawings Paragraph - DRTX
(15):
[0194] FIG. 14 depicts a Western blot showing the binding of Y1 and Y17 to lysate of washed platelets cleaved by mocarhagin and cathepsin G.

Detail Description Paragraph - DETX (7):
[0237] The human platelet derived glycocalicin extracellular fragment was purified from activated platelets. It was digested with various proteases, such as ficin, mocarhagin, cathepsin G, in order to localize precisely the Y1 binding epitope on the glycocalicin molecule. Analysis was performed by the Western blot methodology using the Y1 antibody as a detection tool. In addition, commercially available anti-glycocalicin antibodies (antibodies that are known to bind to different epitopes of glycocalicin) were used in a competition binding assay with the Y1 antibody to determine the Y1 binding epitope on glycocalicin.

Detail Description Paragraph - DETX (119):
[0349] Mocarhagin Cleavage of GPIb--Mapping of the Y1 Epitope

Detail Description Paragraph - DETX (120):
[0350] Mocarhagin [Sigma L4515a] is a cobra venom metalloproteinase that cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, thereby generating two stable products: a .about.45-kDa N-terminal fragment (His1-Glu282), which is released into the supernatant, and a membrane-bound .about.95 kDa C-terminal fragment.

Detail Description Paragraph - DETX (121):
[0351] Washed platelets were treated by mocarhagin, and platelet lysates were electrophoresed on SDS-polyacrylamide gels and transferred to nitrocellulose. Western blot analysis of lysates of mocarhagin-treated washed platelets with Y1 shows a loss of the band corresponding to GPIb.alpha. (135 kDa) and binding of Y1 to the N-terminal .about.45 kDa tryptic fragment. A monoclonal antibody (MCA466S) directed against the C-terminal fragment of GPIb.alpha. reacted with the .about.95 kDa C-terminal fragment, and a monoclonal antibody (S.C.7071) directed against the N-terminal fragment of GPIb.alpha. reacted with the same .about.45 kDa fragment that was recognized by Y1. (FIG. 7).

Detail Description Paragraph - DETX (122):
[0352] Mocarhagin treatment of glycocalicin (soluble, extracellular fragment of GPIb.alpha.) gave similar results to those observed with washed platelets, showing binding of Y1 and monoclonal antibody S.C.7071 to the .about.45 kDa N-terminal cleavage product fragment of GPIb.alpha.. (FIG. 8). These results suggest that the epitope for Y1 is contained within the sequence His1-Glu282.

Detail Description Paragraph - DETX (139):
[0369] These results further support the hypothesis that sulfated tyrosine residues within the specific region are important for Y1 recognition on GPIb. Overall, analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggest that the GPIb.alpha. amino acid sequence Tyr276-Glu-282 is or contains an important epitope for binding of Y1. (FIGS. Tab 1C pages 6 and 7). Further characterization indicated that in addition to residues 276-282 (sulfated anionic sequence) of glycocalicin, upstream amino acids 283-285 are involved in the recognition site of Y1.

Detail Description Paragraph - DETX (332):
[0555] 3.1 Cleavage of Platelets by Mocarhagin

Detail Description Paragraph - DETX (333):
[0556] For mocarhagin digestion, 10.sup.8 washed platelets in TS buffer (0.01 M Tris, 0.15 M sodium chloride, pH 7.4) containing 1 mM calcium chloride were treated with 12 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (340):
[0561] Cleavage of Glycocalicin by Mocarhagin

Detail Description Paragraph - DETX (341):
[0562] For mocarhagin digestion, glycocalicin in TS buffer containing 1 mM calcium chloride was incubated with 10 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (475):
[0668] 18.1: Effect of Mocarhagin on the Mapping of Y1 Epitope

Detail Description Paragraph - DETX (476):
[0669] Mocarhagin, a cobra venom metalloproteinase cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, generates two stable products, a 45-kDa N-terminal fragment (His-1-Glu-282) found in the supernatant and a membrane bound 100 kDa C-terminal fragment.

Detail Description Paragraph - DETX (477):
[0670] Washed platelets were treated by mocarhagin and, platelets lysate were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Analysis of mocarhagin-treated washed platelets by Western blot analysis with Y1-results in loss of the band corresponding to GPb (135 kDa) and, binding of Y17 to the N-terminal 45 kDa tryptic fragment. Monoclonal antibodies, MCA466S directed against the C-terminal fragment of GPIb.alpha. reacted with the 100 kDa C-terminal fragment while, monoclonal antibody S.C.7071 which recognizes the N-terminal of GPIb.alpha. reacted with the same 45 kDa N-terminal fragment that was recognized by Y17 (FIG. 14).

Detail Description Paragraph - DETX (478):
[0671] Mocarhagin treatment of glycocalicin gave results similar to those observed with washed platelets, showing binding of Y1 and monoclonal antibodies, S.C. 7071 to 45 kDa N-terminal cleavage product fragment of GPIb.alpha. (FIG. 8). The results suggest that the epitope for Y17 is contained within the sequence His-1-Glu-282.

Detail Description Paragraph - DETX (480):
[0673] Cathepsin G, a neutrophil serine protease, cleaved glycocalicin

between residues leu-275 and Tyr-276 and a second cleavage site between residues Val-296 and Lys-297. Glycocalicin treated by cathepsin G generated two N-terminal fragments, a small fragment 42 kDa fragment (His1-Leu275) and a large 45 kDa N-terminal fragment (His1-Val-296), in addition to a .about.95 kDa C-terminal fragment. Glycocalicin and glycocalicin fragments generated by cathepsin G digestion were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Y17 bound to the larger fragment (His1-Val-296), but not to the smaller fragment (His1-Leu275). Moreover, monoclonal antibody S.C. 7071 which recognizes an epitope within His1-Leu275 blotted both fragments (FIG. 12). Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the BPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17.

Detail Description Paragraph - DETX (483):

[0674] The effect of Y17-scFv on vWF-dependent agglutination of platelets was tested at different concentrations of Y17. In contrast to Y1, Y17 at a final concentration of 10, 25 or 50 .mu.g/ml did not inhibit vWF-dependent platelet agglutination in washed platelets induced by ristocetin. Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the GPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17 and Y1. Since Y17 does not inhibit platelet aggregation, it seems that Y1 and Y17 do not bind to the same sequences, but to overlapping sequences.

Detail Description Table CWU - DETL (11):

11TABLE 10 Western Blot Analysis with Y1 on SDS-PAGE Reducing Gels Presented Reactivity in Substrate Treatment Condition with Y1 FIG. RP-HPLC KG- O-Sialo 30' at 37.degree. C. Reactivity Tab 2A 1 membrane glycoprotein only with slide 14 fraction endopep- the tidase 120 kDa form RP-HPLC KG- O-Sialo 4 hr at 37.degree. C. No Tab 2A 1 membrane glycoprotein reactivity slide 14 fraction endopep- tidase RP-HPLC KG- aryl-sulfatase 18 hr at 22.degree. C. No Tab 2A 1 membrane reactivity slide 14 fraction RP-HPLC KG- mocarhagin 7' at 37.degree. C. No Tab 2A 1 membrane reactivity slide 14 fraction Glycocalicin O-Sialo 30' at 37.degree. C. Enhanced Tab 2A (GC) glycoprotein binding slide 14 endopep- tidase Heparin - BSA aryl-sulfatase 18 hr at 22.degree. C. Binds to Tab 2A Y1 as slide 16 without treatment

PGPUB-DOCUMENT-NUMBER: 20040001839

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040001839 A1

TITLE: Multimers - isolated molecules comprising epitopes containing sulfated moieties, antibodies to such epitopes, and uses thereof

PUBLICATION-DATE: January 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Levanon, Avigdor	Rehovot		IL	
Hagay, Yocheved	Rehovot		IL	
Plaksin, Daniel	Rehovot		IL	
Vogel, Tikva	Rehovot		IL	
Nimrod, Abraham	Rehovot		IL	
Mar-Haim, Hagit	Aseret		IL	
Szanthon, Ester	Rehovot		IL	
Richter, Tamar	Nes Tziona		IL	
Amit, Boaz	Kiron		IL	
Cooperman, Lena	Rishon Lezion		IL	
Peretz, Tuvia	Hod Hasharon		IL	
Lazarovits, Janette	Reut		IL	

APPL-NO: 10/ 029988

DATE FILED: December 31, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60258948 20001229 US

US-CL-CURRENT: 424/178.1, 530/391.1

ABSTRACT:

The present invention provides epitopes present on cancer cells and important in physiological phenomena such as cell rolling, metastasis, and inflammation. Therapeutic and diagnostic methods and compositions using antibodies capable of binding to the epitopes are provided. Methods and compositions according to the present invention can be used in diagnosis of and therapy for such diseases as cancer, including tumor growth and metastasis, leukemia, auto-immune disease, and inflammatory disease

FIELD OF THE INVENTION

[0001] This application is a Continuation-in-Part application of U.S. provisional application Serial No. 60/258,948, filed on Dec. 29, 2000, the subject matter of which is incorporated by reference hereto.

---------- KWIC --------

Brief Description of Drawings Paragraph - DRTX (8):

[0160] FIG. 7 depicts a Western blot demonstrating that Y1 binds the N-terminal (His1-Glu282) fragment of platelet GPIb.alpha. after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX (9):
[0161] FIG. 8 depicts a Western blot showing binding of Y1 and Y17 to glycocalicin after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX (14):
[0166] FIG. 13 depicts a Western blot demonstrating that cleavage of glycocalicin by mocarhagin and cathepsin G abolishes binding of Y1.

Brief Description of Drawings Paragraph - DRTX (15):
[0167] FIG. 14 depicts a Western blot showing the binding of Y1 and Y17 to lysate of washed platelets cleaved by mocarhagin and cathepsin G.

Detail Description Paragraph - DETX (7):
[0210] The human platelet derived glycocalicin extracellular fragment was purified from activated platelets. It was digested with various proteases, such as ficin, mocarhagin, cathepsin G, in order to localize precisely the Y1 binding epitope on the glycocalicin molecule. Analysis was performed by the Western blot methodology using the Y1 antibody as a detection tool. In addition, commercially available anti-glycocalicin antibodies (antibodies that are known to bind to different epitopes of glycocalicin) were used in a competition binding assay with the Y1 antibody to determine the Y1 binding epitope on glycocalicin.

Detail Description Paragraph - DETX (119):
[0322] Mocarhagin Cleavage of GPIb--Mapping of the Y1 Epitope

Detail Description Paragraph - DETX (120):
[0323] Mocarhagin [Sigma L4515a] is a cobra venom metalloproteinase that cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, thereby generating two stable products: a .about.45-kDa N-terminal fragment (His1-Glu282), which is released into the supernatant, and a membrane-bound .about.95 kDa C-terminal fragment.

Detail Description Paragraph - DETX (121):
[0324] Washed platelets were treated by mocarhagin, and platelet lysates were electrophoresed on SDS-polyacrylamide gels and transferred to nitrocellulose. Western blot analysis of lysates of mocarhagin-treated washed platelets with Y1 shows a loss of the band corresponding to GPIb.alpha. (135 kDa) and binding of Y1 to the N-terminal .about.45 kDa tryptic fragment. A monoclonal antibody (MCA466S) directed against the C-terminal fragment of GPIba reacted with the .about.95 kDa C-terminal fragment, and a monoclonal antibody (S.C.7071) directed against the N-terminal fragment of GPIb.alpha. reacted with the same .about.45 kDa fragment that was recognized by Y1. (FIG. 7).

Detail Description Paragraph - DETX (122):
[0325] Mocarhagin treatment of glycocalicin (soluble, extracellular fragment of GPIb.alpha.) gave similar results to those observed with washed platelets, showing binding of Y1 and monoclonal antibody S.C.7071 to the .about.45 kDa N-terminal cleavage product fragment of GPIb.alpha.. (FIG. 8). These results suggest that the epitope for Y1 is contained within the sequence His1-Glu282.

Detail Description Paragraph - DETX (139):

[0342] These results further support the hypothesis that sulfated tyrosine residues within the specific region are important for Y1 recognition on GPIb. Overall, analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggest that the GPIb.alpha. amino acid sequence Tyr276-Glu-282 is or contains an important epitope for binding of Y1. (FIGS. Tab 1C pages 6 and 7). Further characterization indicated that in addition to residues 276-282 (sulfated anionic sequence) of glycocalicin, upstream amino acids 283-285 are involved in the recognition site of Y 1.

Detail Description Paragraph - DETX (333):
[0529] 3.1 Cleavage of Platelets by Mocarhagin

Detail Description Paragraph - DETX (334):
[0530] For mocarhagin digestion, 10.sup.8 washed platelets in TS buffer (0.01 M Tris, 0.15 M sodium chloride, pH 7.4) containing 1 mM calcium chloride were treated with 12 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (341):
[0535] Cleavage of Glycocalicin by Mocarhagin

Detail Description Paragraph - DETX (342):
[0536] For mocarhagin digestion, glycocalicin in TS buffer containing 1 mM calcium chloride was incubated with 10 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (483):
[0649] 18.1: Effect of Mocarhagin on the Mapping of Y1 Epitope

Detail Description Paragraph - DETX (484):
[0650] Mocarhagin, a cobra venom metalloproteinase cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, generates two stable products, a 45-kDa N-terminal fragment (His-1-Glu-282) found in the supernatant and a membrane bound 100 kDa C-terminal fragment.

Detail Description Paragraph - DETX (485):
[0651] Washed platelets were treated by mocarhagin and, platelets lysate were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Analysis of mocarhagin-treated washed platelets by Western blot analysis with Y1-results in loss of the band corresponding to GPIb (135 kDa) and, binding of Y17 to the N-terminal 45 kDa tryptic fragment. Monoclonal antibodies, MCA466S directed against the C-terminal fragment of GPIb.alpha. reacted with the 100 kDa C-terminal fragment while, monoclonal antibody S.C.7071 which recognizes the N-terminal of GPIb.alpha. reacted with the same 45 kDa N-terminal fragment that was recognized by Y17 (FIG. 14).

Detail Description Paragraph - DETX (486):
[0652] Mocarhagin treatment of glycocalicin gave results similar to those observed with washed platelets, showing binding of Y1 and monoclonal antibodies, S.C. 7071 to 45 kDa N-terminal cleavage product fragment of GPIb.alpha. (FIG. 8). The results suggest that the epitope for Y17 is contained within the sequence His-1-Glu-282.

Detail Description Paragraph - DETX (488):
[0654] Cathepsin G, a neutrophil serine protease, cleaved glycocalicin between residues leu-275 and Tyr-276 and a second cleavage site between residues Val-296 and Lys-297. Glycocalicin treated by cathepsin G generated

two N-terminal fragments, a small fragment 42 kDa fragment (His1-Leu275) and a large 45 kDa N-terminal fragment (His1-Val-296), in addition to a .about.95 kDa C-terminal fragment. Glycocalicin and glycocalicin fragments generated by cathepsin G digestion were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Y17 bound to the larger fragment (His1-Val-296), but not to the smaller fragment (His1-Leu275). Moreover, monoclonal antibody S.C. 7071 which recognizes an epitope within His1-Leu275 blotted both fragments (FIG. 12). Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the BPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17.

Detail Description Paragraph - DETX (491):

[0655] The effect of Y17-scFv on vWF-dependent agglutination of platelets was tested at different concentrations of Y17. In contrast to Y1, Y17 at a final concentration of 10, 25 or 50 .mu.g/ml did not inhibit vWF-dependent platelet agglutination in washed platelets induced by ristocetin. Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the GPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17 and Y1. Since Y17 does not inhibit platelet aggregation, it seems that Y1 and Y17 do not bind to the same sequences, but to overlapping sequences.

Detail Description Table CWU - DETL (11):

11TABLE 10 Western Blot Analysis with Y1 on SDS-PAGE Reducing Gels Reactivity Presented with in Substrate Treatment Condition Y1 FIG. RP-HPLC KG-1 O-Sialo 30' at Reactivity Tab 2A membrane glycoprotein 37.degree. C. only with slide 14 fraction endopeptidase the 120 kDa form RP-HPLC KG-1 O-Sialo 4 hr at No Tab 2A membrane glycoprotein 37.degree. C. reactivity slide 14 fraction endopeptidase RP-HPLC KG-1 aryl-sulfatase 18 hr at No Tab 2A membrane 22.degree. C. reactivity slide 14 fraction RP-HPLC KG-1 mocarhagin 7' at No Tab 2A membrane 37.degree. C. reactivity slide 14 fraction Glycocalicin O-Sialo 30' at Enhanced Tab 2A (GC) glycoprotein 37.degree. C. binding slide 14 endopeptidase Heparin - BSA aryl-sulfatase 18 hr at Binds to Tab 2A 22.degree. C. Y1 as slide 16 without treatment

PGPUB-DOCUMENT-NUMBER: 20040001822

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20040001822 A1

TITLE: Y1-isolated molecules comprising epitopes containing sulfated moieties, antibodies to such epitopes, and uses thereof

PUBLICATION-DATE: January 1, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Levanon, Avigdor	Rehovot		IL	
Hagay, Yocheved	Rehovot		IL	
Plaksin, Daniel	Rehovot		IL	
Vogel, Tikva	Rehovot		IL	
Nimrod, Abraham	Rehovot		IL	
Mar-Haim, Hagit	Aseret		IL	
Szanthon, Esther	Rehovot		IL	
Richter, Tamar	Nes Tziona		IL	
Amit, Boaz	Kiron		IL	
Cooperman, Lena	Rishon Lezion		IL	
Peretz, Tuvia	Hod Hasharon		IL	
Lazarovits, Janette	Reut		IL	

APPL-NO: 10/ 032037

DATE FILED: December 31, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60258948 20001229 US

US-CL-CURRENT: 424/130.1, 424/450 , 424/85.4 , 514/183 , 514/323 , 514/575 , 514/59 , 514/8 , 530/359 , 530/388.1

ABSTRACT:

The present invention provides epitopes present on cancer cells and important in physiological phenomena such as cell rolling, metastasis, and inflammation. Therapeutic and diagnostic methods and compositions using antibodies capable of binding to the epitopes are provided. Methods and compositions according to the present invention can be used in diagnosis of and therapy for such diseases as cancer, including tumor growth and metastasis, leukemia, auto-immune disease, and inflammatory disease.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application is a Continuation-in-Part application of U.S. provisional application Serial No. 60/258,948, filed on Dec. 29, 2000, the subject matter of which is incorporated by reference hereto.

---------- KWIC --------

Brief Description of Drawings Paragraph - DRTX

(8):
[0187] FIG. 7 depicts a Western blot demonstrating that Y1 binds the N-terminal (His 1-Glu 282) fragment of platelet GPIb.alpha. after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX
(9):
[0188] FIG. 8 depicts a Western blot showing binding of Y1 and Y17 to glycocalicin after cleavage by mocarhagin.

Brief Description of Drawings Paragraph - DRTX
(14):
[0193] FIG. 13 depicts a Western blot demonstrating that cleavage of glycocalicin by mocarhagin and cathepsin G abolishes binding of Y1.

Brief Description of Drawings Paragraph - DRTX
(15):
[0194] FIG. 14 depicts a Western blot showing the binding of Y1 and Y17 to lysate of washed platelets cleaved by mocarhagin and cathepsin G.

Detail Description Paragraph - DETX (7):
[0237] The human platelet derived glycocalicin extracellular fragment was purified from activated platelets. It was digested with various proteases, such as ficin, mocarhagin, cathepsin G, in order to localize precisely the Y1 binding epitope on the glycocalicin molecule. Analysis was performed by the Western blot methodology using the Y1 antibody as a detection tool. In addition, commercially available anti-glycocalicin antibodies (antibodies that are known to bind to different epitopes of glycocalicin) were used in a competition binding assay with the Y1 antibody to determine the Y1 binding epitope on glycocalicin.

Detail Description Paragraph - DETX (119):
[0349] Mocarhagin Cleavage of GPIb--Mapping of the Y1 Epitope

Detail Description Paragraph - DETX (120):
[0350] Mocarhagin [Sigma L4515a] is a cobra venom metalloproteinase that cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, thereby generating two stable products: a .about.45-kDa N-terminal fragment (His1-Glu282), which is released into the supernatant, and a membrane-bound .about.95 kDa C-terminal fragment.

Detail Description Paragraph - DETX (121):
[0351] Washed platelets were treated by mocarhagin, and platelet lysates were electrophoresed on SDS-polyacrylamide gels and transferred to nitrocellulose. Western blot analysis of lysates of mocarhagin-treated washed platelets with Y1 shows a loss of the band corresponding to GPIb.alpha. (135 kDa) and binding of Y1 to the N-terminal .about.45 kDa tryptic fragment. A monoclonal antibody (MCA466S) directed against the C-terminal fragment of GPIb.alpha. reacted with the .about.95 kDa C-terminal fragment, and a monoclonal antibody (S.C.7071) directed against the N-terminal fragment of GPIb.alpha. reacted with the same .about.45 kDa fragment that was recognized by Y1. (FIG. 7).

Detail Description Paragraph - DETX (122):
[0352] Mocarhagin treatment of glycocalicin (soluble, extracellular fragment of GPIb.alpha.) gave similar results to those observed with washed platelets, showing binding of Y1 and monoclonal antibody S.C.7071 to the .about.45 kDa N-terminal cleavage product fragment of GPIb.alpha.. (FIG. 8). These results suggest that the epitope for Y1 is contained within the sequence His1-Glu282.

Detail Description Paragraph - DETX (139):
[0369] These results further support the hypothesis that sulfated tyrosine residues within the specific region are important for Y1 recognition on GPIb. Overall, analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggest that the GPIb.alpha. amino acid sequence Tyr276-Glu-282 is or contains an important epitope for binding of Y1. (FIGS. Tab 1C pages 6 and 7). Further characterization indicated that in addition to residues 276-282 (sulfated anionic sequence) of glycocalicin, upstream amino acids 283-285 are involved in the recognition site of Y 1.

Detail Description Paragraph - DETX (334):
[0560] 3.1 Cleavage of Platelets by Mocarhagin

Detail Description Paragraph - DETX (335):
[0561] For mocarhagin digestion, 10.sup.8 washed platelets in TS buffer (0.01 M Tris, 0.15 M sodium chloride, pH 7.4) containing 1 mM calcium chloride were treated with 12 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (342):
[0567] Cleavage of Glycocalicin by Mocarhagin

Detail Description Paragraph - DETX (343):
[0568] For mocarhagin digestion, glycocalicin in TS buffer containing 1 mM calcium chloride was incubated with 10 .mu.g/ml mocarhagin (final concentration) for 1 hour at 22.degree. C. and digestion was stopped by adding EDTA to 0.01 M.

Detail Description Paragraph - DETX (473):
[0684] 18.1: Effect of Mocarhagin on the Mapping of Y1 Epitope

Detail Description Paragraph - DETX (474):
[0685] Mocarhagin, a cobra venom metalloproteinase cleaves platelet GPIb.alpha. specifically at a single site between residues glu-282 and asp-283, generates two stable products, a 45-kDa N-terminal fragment (His-1-Glu-282) found in the supernatant and a membrane bound 100 kDa C-terminal fragment.

Detail Description Paragraph - DETX (475):
[0686] Washed platelets were treated by mocarhagin and, platelets lysate were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Analysis of mocarhagin-treated washed platelets by Western blot analysis with Y1-results in loss of the band corresponding to GPIb (135 kDa) and, binding of Y17 to the N-terminal 45 kDa tryptic fragment. Monoclonal antibodies, MCA466S directed against the C-terminal fragment of GPIb.alpha. reacted with the 100 kDa C-terminal fragment while, monoclonal antibody S.C.7071 which recognizes the N-terminal of GPIb.alpha. reacted with the same 45 kDa N-terminal fragment that was recognized by Y17 (FIG. 14).

Detail Description Paragraph - DETX (476):
[0687] Mocarhagin treatment of glycocalicin gave results similar to those observed with washed platelets, showing binding of Y1 and monoclonal antibodies, S.C. 7071 to 45 kDa N-terminal cleavage product fragment of GPIb.alpha. (FIG. 8). The results suggest that the epitope for Y17 is contained within the sequence His-1-Glu-282.

Detail Description Paragraph - DETX (478):
[0689] Cathepsin G, a neutrophil serine protease, cleaved glycocalicin

between residues leu-275 and Tyr-276 and a second cleavage site between residues Val-296 and Lys-297. Glycocalicin treated by cathepsin G generated two N-terminal fragments, a small fragment 42 kDa fragment (His1-Leu275) and a large 45 kDa N-terminal fragment (His1-Val-296), in addition to a 95 kDa C-terminal fragment. Glycocalicin and glycocalicin fragments generated by cathepsin G digestion were separated on SDS-polyacrylamide gels and transferred to nitrocellulose. Y17 bound to the larger fragment (His1-Val-296), but not to the smaller fragment (His1-Leu275). Moreover, monoclonal antibody S.C. 7071 which recognizes an epitope within His1-Leu275 blotted both fragments (FIG. 12). Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the BPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17.

Detail Description Paragraph - DETX (481):

[0691] The effect of Y17-scFv on vWF-dependent agglutination of platelets was tested at different concentrations of Y17. In contrast to Y1, Y17 at a final concentration of 10, 25 or 50 .mu.g/ml did not inhibit vWF-dependent platelet agglutination in washed platelets induced by ristocetin. Analysis of N-terminal peptide proteolytic fragments of mocarhagin and cathepsin G suggests that the GPIb.alpha. amino acid sequence Tyr-276-Glu-282 is an important recognition motif for binding of Y17 and Y1. Since Y17 does not inhibit platelet aggregation, it seems that Y1 and Y17 do not bind to the same sequences, but to overlapping sequences.

Detail Description Table CWU - DETL (11):

11TABLE 10 Presented Reactivity in Substrate Treatment Condition with Y1 FIG. RP-HPLC KG- O-Sialo 30' at 37.degree. C. Reactivity Tab 2A 1 membrane glycoprotein only slide 14 fraction endopeptidase with the 120 kDa form RP-HPLC KG- O-Sialo 4 hr at 37.degree. C. No Tab 2A 1 membrane glycoprotein reactivity slide 14 fraction endopeptidase RP-HPLC KG- aryl-sulfatase 18 hr at 22.degree. C. No Tab 2A 1 membrane reactivity slide 14 fraction RP-HPLC KG- Mocarhagin 7' at 37.degree. C. No Tab 2A 1 membrane reactivity slide 14 fraction Glycocalicin O-Sialo 30' at 37.degree. C. Enhanced Tab 2A (GC) glycoprotein binding slide 14 endopeptidase Heparin - aryl-sulfatase 18 hr at 22.degree. C. Binds to Tab 2A BSA Y1 as slide 16 without treatment

PGPUB-DOCUMENT-NUMBER: 20030232753

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030232753 A1

TITLE: Combined tissue factor methods for coagulation and tumor treatment

PUBLICATION-DATE: December 18, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thorpe, Philip E.	Dallas	TX	US	
King, Steven W.	Foothill Ranch	CA	US	
Gao, Boning	Dallas	TX	US	

APPL-NO: 10/ 375741

DATE FILED: February 27, 2003

RELATED-US-APPL-DATA:

child 10375741 A1 20030227

parent continuation-of 09573835 20000518 US PENDING

child 09573835 20000518 US

parent division-of 09009822 19980120 US GRANTED

parent-patent 6156321 US

non-provisional-of-provisional 60042427 19970327 US

non-provisional-of-provisional 60036205 19970127 US

non-provisional-of-provisional 60035920 19970122 US

US-CL-CURRENT: 514/12

ABSTRACT:

The invention embodies the surprising discovery that Tissue Factor (TF) compositions and variants thereof specifically localize to the blood vessels within a vascularized tumor following systemic administration. The invention therefore provides methods and compositions comprising coagulant-deficient Tissue Factor for use in effecting specific coagulation and for use in tumor treatment. The TF compositions and methods of present invention may be used alone, as TF conjugates with improved half-life, or in combination with other agents, such as conventional chemotherapeutic drugs, targeted immunotoxins, targeted coaguligands, and/or in combination with Factor VIIa (FVIIa) or FVIIa activators.

[0001] The present application is a non-provisional application directed to the subject matter of provisional application Serial No. 60/042,427 (Attorney

Docket No. UTSD:517PZ3), filed Mar. 27, 1997; provisional application Serial No. 60/036,205 (Attorney Docket No. UTSD:517PZ2), filed Jan. 27, 1997; and provisional application Serial No. 60/035,920 (Attorney Docket No. UTSD:517PZ1), filed Jan. 22, 1997; the entire disclosures of each of which provisional applications are incorporated herein by reference without disclaimer.

---------- KWIC ---------

Detail Description Paragraph - DETX (263):
[0351] Coagulants, such as thrombin, Factor IX/IXa, Factor X/Xa, plasmin and metalloproteinases, such as interstitial collagenases, stromelysins and gelatinases, also act to induce certain markers. In particular, E-selectin, P-selectin, PDGF and ICAM-1 are induced by thrombin (Sugama et. al., 1992; Shankar et. al., 1994).

Detail Description Paragraph - DETX (331):
[0419] Russell's viper venom was shown to contain a coagulant protein by Williams and Esnouf in 1962. Kisiel (1979) isolated a venom glycoprotein that activates Factor V; and Di Scipio ey al. (1977) showed that a protease from the venom activates human Factor X. The Factor X activator is the component contemplated for use in this invention.

PGPUB-DOCUMENT-NUMBER: 20030219441

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030219441 A1

TITLE: Combined methods and compositions for coagulation and tumor treatment

PUBLICATION-DATE: November 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Thorpe, Philip E.	Dallas	TX	US	
Edgington, Thomas S.	La Jolla	CA	US	

APPL-NO: 10/ 375716

DATE FILED: February 27, 2003

RELATED-US-APPL-DATA:

child 10375716 A1 20030227

parent continuation-of 09483679 20000114 US PENDING

child 09483679 20000114 US

parent continuation-of 08482369 19950607 US GRANTED

parent-patent 6093399 US

child 08482369 19950607 US

parent continuation-in-part-of 08273567 19940711 US ABANDONED

child 08273567 19940711 US

parent continuation-in-part-of 08205330 19940302 US GRANTED

parent-patent 5855866 US

child 08205330 19940302 US

parent continuation-in-part-of 07846349 19920305 US ABANDONED

US-CL-CURRENT: 424/155.1, 530/388.8

ABSTRACT:

Disclosed are various compositions and methods for use in achieving specific blood coagulation. This is exemplified by the specific in vivo coagulation of tumor vasculature, causing tumor regression, through the site-specific delivery of a coagulant using a bispecific antibody.

[0001] The present application is a continuation-in-part of co-pending U.S.

patent application Ser. No. 08/273,567, filed Jun. 11, 1994; which is a continuation-in-part of co-pending U.S. patent application Ser. No. 08/205,330,.filed, Mar. 2, 1994; which is a continuation-in-part of U.S. Ser. No. 07/846,349, filed Mar. 5, 1992. The entire text and figures of the above-referenced disclosures are specifically incorporated herein by reference without disclaimer.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (44):
[0043] Further inducible antigens include those inducible by a coagulant, such as by thrombin, Factor IX/IXa, Factor X/Xa, plasmin or a metalloproteinase (matrix metalloproteinase, MMP). Generally, antigens inducible by thrombin will be used. This group of antigens includes P-selectin, E-selectin, PDGF and ICAM-1, with the induction and targeting of P-selectin and/or E-selectin being generally preferred.

Detail Description Paragraph - DETX (77):
[0179] Coagulants, such as thrombin, Factor IX/IXa, Factor X/Xa, plasmin and metalloproteinases, such as interstitial collagenases, stromelysins and gelatinases, also act to induce certain markers. In particular, E-selectin, P-selectin, PDGF and ICAM-1 are induced by thrombin (Sugama et. al., 1992; Shankar et. al., 1994).

Detail Description Paragraph - DETX (144):
[0246] Russell's viper venom was shown to contain a coagulant protein by Williams and Esnouf in 1962. Kisiel (1979) isolated a venom glycoprotein that activates Factor V; and Di Scipio et al. (1977) showed that a protease from the venom activates human Factor X. The Factor X activator is the component contemplated for use in this invention.

PGPUB-DOCUMENT-NUMBER: 20030166194

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030166194 A1

TITLE: DNA clone of human tissue factor inhibitor

PUBLICATION-DATE: September 4, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wun, Tze Chein	Ballwin	MO	US	
Kretzmer, Kuniko K.	Wildwood	MO	US	
Broze, George J. JR.	St. Louis	MO	US	

APPL-NO: 10/ 377817

DATE FILED: March 4, 2003

RELATED-US-APPL-DATA:

child 10377817 A1 20030304

parent continuation-of 09627676 20000728 US GRANTED

parent-patent 6534276 US

child 09627676 20000728 US

parent continuation-of 09054782 19980403 US GRANTED

parent-patent 6171587 US

child 09054782 19980403 US

parent continuation-of 08463323 19950605 US GRANTED

parent-patent 5849875 US

child 08463323 19950605 US

parent continuation-of 08355351 19941213 US ABANDONED

child 08355351 19941213 US

parent continuation-of 08093285 19930715 US GRANTED

parent-patent 5466783 US

child 08093285 19930715 US

parent continuation-of 07566280 19900813 US ABANDONED

child 07566280 19900813 US

parent division-of 07123753 19871123 US GRANTED

parent-patent 4966852 US

child 07123753 19871123 US

parent continuation-in-part-of 07077366 19870723 US ABANDONED

US-CL-CURRENT: 435/184, 536/23.2

ABSTRACT:

A cDNA clone having a base sequence for human tissue factor inhibitor (TFI) has been developed and characterized and the amino acid sequence of the TFI has been determined.

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This is a continuation-in-part of copending application Ser. No. 77,366, filed Jul. 23, 1987.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX (8):

[0021] FIG. 6 shows an alignment of the basic protease inhibitor domains of TFI with other basic protease inhibitors. All the sequences except TFI were obtained from the National Biomedical Research Foundation Protein Sequence Database (Georgetown University, Washington, D.C., release 13, June 1987). 1. Bovine basic protease inhibitor precursor; 2. Bovine colostrum trypsin inhibitor; 3. Bovine serum basic protease inhibitor; 4. Edible snail isoinhibitor K; 5. Red sea turtle basic protease inhibitor (only amino acids 1-79 presented); 6. Western sand viper venom basic protease inhibitor I; 7. Ringhals venom basic protease inhibitor II; 8. Cape cobra venom basic protease inhibitor II; 9. Russell's viper venom basic protease inhibitor II; 10. Sand viper venom basic protease inhibitor III; 11. Eastern green mamba venom basic protease inhibitor I homolog; 12. Black mamba venom basic protease inhibitor B; 13. Black mamba venom basic protease inhibitor E; 14. Black mamba venom basic protease inhibitor I; 15. Black mamba venom basic protease inhibitor K; 16. .beta.-1-Bungarotoxin B chain (minor); 17. .beta.-1-Bungarotoxin B chain (major); 18. .beta.-2-Bungarotoxin B chain; 19. Horse inter-.alpha.-trypsin inhibitor [amino acids 1-57(1); 58-123 (2)]; 20. Pig inter-.alpha.-trypsin inhibitor [amino acids 1-57(1); 58-123(2)]; 21. Bovine inter-.alpha.-trypsin inhibitor [amino acids 1-57(1); 58-123(2)]; 22. Human .alpha.-1-microglobulin/inter-.alpha.-trypsin inhibitor precursor [amino acids 227-283(1); 284-352(2)]; 23. TFI [amino acids 47-117(1); 118-188(2); 210-280(3)]. Gaps were included in 16, 17, 18 to achieve best alignment. Standard one letter codes for amino acids are used.

US-PAT-NO: 6749853

DOCUMENT-IDENTIFIER: US 6749853 B1

TITLE: Combined methods and compositions for coagulation and tumor treatment

DATE-ISSUED: June 15, 2004

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Thorpe; Philip E.	Cape Elizabeth	ME	N/A	N/A
Edgington; Thomas S.	La Jolla	CA	N/A	N/A

APPL-NO: 09/ 483679

DATE FILED: January 14, 2000

PARENT-CASE:

The present application is a continuation of application Ser. No. 08/482,369, filed Jun. 7, 1995 (now issued as U.S. Pat. No. 6,093,399); which is a continuation-in-part of U.S. patent application Ser. No. 08/273,567, filed Jul. 11, 1994 now abandoned; which is a continuation-in-part of U.S. patent application Ser. No. 08/205,330, filed Mar. 2, 1994; (now issued as U.S. Pat. No. 5,855,866) which is a continuation-in-part of U.S. Ser. No. 07/846,349, filed Mar. 5, 1992 now abandoned. The entire text and figures of the above-referenced disclosures are specifically incorporated herein by reference without disclaimer.

US-CL-CURRENT: 424/182.1, 424/178.1 , 530/387.1 , 530/387.3

ABSTRACT:

Disclosed are various compositions and methods for use in achieving specific blood coagulation. This is exemplified by the specific in vivo coagulation of tumor vasculature, causing tumor regression, through the site-specific delivery of a coagulant using a bispecific antibody.

47 Claims, 11 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 8

---------- KWIC --------

Brief Summary Text - BSTX (44):

Further inducible antigens include those inducible by a coagulant, such as by thrombin, Factor IX/IXa, Factor X/Xa, plasmin or a metalloproteinase (matrix metalloproteinase, MMP). Generally, antigens inducible by thrombin will be used. This group of antigens includes P-selectin, E-selectin, PDGF and ICAM-1, with the induction and targeting of P-selectin and/or E-selectin being generally preferred.

Detailed Description Text - DETX (76):

Coagulants, such as thrombin, Factor IX/IXa, Factor X/Xa, plasmin and metalloproteinases, such as interstitial collagenases, stromelysins and gelatinases, also act to induce certain markers. In particular, E-selectin, P-selectin, PDGF and ICAM-1 are induced by thrombin (Sugama et. al., 1992; Shankar et. al., 1994).

Detailed Description Text - DETX (142):

Russell's viper venom was shown to contain a coagulant protein by Williams and Esnouf in 1962. Kisiel (1979) isolated a venom glycoprotein that activates Factor V; and Di Scipio et al. (1977) showed that a protease from the venom activates human Factor X. The Factor X activator is the component contemplated for use in this invention.

US-PAT-NO: 6607897

DOCUMENT-IDENTIFIER: US 6607897 B2

TITLE: Recombinant proCVF

DATE-ISSUED: August 19, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vogel; Carl-Wilhelm	Hamburg	N/A	N/A	DE
Bredehorst; Reinhard	Hamburg	N/A	N/A	DE
Fritzinger; David	Alexandria	VA	N/A	N/A
Kock; Michael	Hamburg	N/A	N/A	DE

APPL-NO: 09/ 925442

DATE FILED: August 10, 2001

PARENT-CASE:

The present application is a Divisional application of Ser. No. 09/017,947 filed Feb. 3, 1998, U.S. Pat. No. 6,303,754 which is a Divisional application of Ser. No. 08/662,227 filed Jun. 14, 1996, U.S. Pat. No. 5,922,320.

US-CL-CURRENT: 435/69.1, 424/94.64 , 435/226 , 435/252.3 , 435/320.1 , 435/325 , 514/12 , 514/8 , 530/380 , 530/395 , 536/23.2 , 536/23.5

ABSTRACT:

Recombinant proCVF exhibits substantially the same activity as CVF and is useful for lowering complement activity.

20 Claims, 38 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 32

---------- KWIC ---------

Detailed Description Text - DETX (40):

Recently, protease activities have been characterized in cobra venom that are able to cleave human C3 into a form that resembles C3b functionally, but has a similar subunit structure to CVF1 (O'Keefe, M. C., et al, 1988, J. Biol. Chem. 263:12690). Since this activity appears to be specific, and not just a random protease, it is possible that this protease serves in the maturation pathway of CVF1. Comparing the venom protease cleavage sites in human C3 to the processing sites in CVF1 shows that the enzyme cleaves human C3 at a position 11 amino acid residues downstream from the actual CVF1 processing site at the N-terminus of the .gamma.-chain, though the venom protease site appears to be in the middle of one of the proposed Factor B binding sites. The second venom protease cleavage site is in a position similar to the C-terminus of the .gamma.-chain, though this position has not been mapped in CVF1. The third

venom protease cleavage site is in position 71 amino acids downstream from the N-terminus of the .beta.-chain.

Detailed Description Text - DETX (48):

Further, proCVF may be processed from the pre-pro-form by treatment with either whole cobra venom or the purified proteases from cobra venom, as described in the Doctoral thesis of M. Clare O'Keefe, Georgetown University, 1991. Thus, active proCVF may be obtained even when produced by a host incapable of the proper post-translational processing. Of course, in some expression systems proCVF will be secreted by the host even though the DNA encodes pre-proCVF.

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  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 10:33:04 ON 16 JUN 2004

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FULL ESTIMATED COST                                         0.21       0.21

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ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

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FILE 'BIOTECHDS'
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FILE 'BIOSIS'
L53         91 L41 AND L5

FILE 'EMBASE'
L54         59 L42 AND L6

FILE 'HCAPLUS'
L55         78 L43 AND L7

FILE 'NTIS'
L56          0 L44 AND L8
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FILE 'ESBIOBASE'
L57         38 L45 AND L9

FILE 'BIOTECHNO'
L58         29 L46 AND L10

FILE 'WPIDS'
L59         20 L47 AND L11

TOTAL FOR ALL FILES
L60        551 L48 AND L12

=> s mocarhagin
FILE 'MEDLINE'
L61         20 MOCARHAGIN

FILE 'SCISEARCH'
L62         19 MOCARHAGIN

FILE 'LIFESCI'
L63          5 MOCARHAGIN

FILE 'BIOTECHDS'
L64          1 MOCARHAGIN

FILE 'BIOSIS'
L65         24 MOCARHAGIN

FILE 'EMBASE'
L66         17 MOCARHAGIN

FILE 'HCAPLUS'
L67         23 MOCARHAGIN

FILE 'NTIS'
L68          0 MOCARHAGIN

FILE 'ESBIOBASE'
L69         14 MOCARHAGIN

FILE 'BIOTECHNO'
L70          9 MOCARHAGIN

FILE 'WPIDS'
L71          2 MOCARHAGIN

TOTAL FOR ALL FILES
L72        134 MOCARHAGIN

=> s (l24 or l36 or l60 or l72) not 1999-2004/py
FILE 'MEDLINE'
       2798713 1999-2004/PY
L73         49 (L13 OR L25 OR L49 OR L61) NOT 1999-2004/PY

FILE 'SCISEARCH'
       5393010 1999-2004/PY
L74         47 (L14 OR L26 OR L50 OR L62) NOT 1999-2004/PY

FILE 'LIFESCI'
        562403 1999-2004/PY
L75         13 (L15 OR L27 OR L51 OR L63) NOT 1999-2004/PY

FILE 'BIOTECHDS'
        101830 1999-2004/PY
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L76          3 (L16 OR L28 OR L52 OR L64) NOT 1999-2004/PY

FILE 'BIOSIS'
       2938645 1999-2004/PY
L77          59 (L17 OR L29 OR L53 OR L65) NOT 1999-2004/PY

FILE 'EMBASE'
       2460677 1999-2004/PY
L78          36 (L18 OR L30 OR L54 OR L66) NOT 1999-2004/PY

FILE 'HCAPLUS'
       5166091 1999-2004/PY
L79          53 (L19 OR L31 OR L55 OR L67) NOT 1999-2004/PY

FILE 'NTIS'
         94742 1999-2004/PY
L80           0 (L20 OR L32 OR L56 OR L68) NOT 1999-2004/PY

FILE 'ESBIOBASE'
       1563021 1999-2004/PY
L81          18 (L21 OR L33 OR L57 OR L69) NOT 1999-2004/PY

FILE 'BIOTECHNO'
        611346 1999-2004/PY
L82          19 (L22 OR L34 OR L58 OR L70) NOT 1999-2004/PY

FILE 'WPIDS'
       4591795 1999-2004/PY
L83           0 (L23 OR L35 OR L59 OR L71) NOT 1999-2004/PY

TOTAL FOR ALL FILES
L84        297 (L24 OR L36 OR L60 OR L72) NOT 1999-2004/PY

=> dup rem l84
PROCESSING COMPLETED FOR L84
L85          120 DUP REM L84 (177 DUPLICATES REMOVED)

=> d tot

L85   ANSWER 1 OF 120  BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
TI    Isolated mocarhagin cobra venom
      protease, and nucleic acids encoding it;
         Mozambiquan spitting cobra venom recombinant
         metallo protease preparation by vector-mediated gene
         transfer and expression in host cell, used for inflammatory disease
         therapy
AU    Boodhoo A; Seehra J S; Shaw G; Sako D
AN    1999-00528  BIOTECHDS
PI    WO 9846771 22 Oct 1998

L85  ANSWER 2 OF 120     MEDLINE on STN
TI   A balance of opposing signals within the cytoplasmic tail controls the
     lysosomal targeting of P-selectin.
SO   Journal of biological chemistry, (1998 Oct 23) 273 (43) 27896-903.
     Journal code: 2985121R. ISSN: 0021-9258.
AU   Blagoveshchenskaya A D; Hewitt E W; Cutler D F
AN   1998447632     MEDLINE

L85  ANSWER 3 OF 120  LIFESCI    COPYRIGHT 2004 CSA on STN
TI   Modulation of Lipopolysaccharide-Induced Monocyte Activation by
     Heparin-Binding Protein and Fucoidan
SO   Infection and Immunity, (19981200) vol. 66, no. 12, pp. 5842-5847.
     ISSN: 0019-9567.
AU   Heinzelmann, M.; Polk, H.C.,Jr.; Miller, F.N.
```

AN 1999:29079 LIFESCI

L85 ANSWER 4 OF 120 BIOTECHDS COPYRIGHT 2004 THOMSON DERWENT/ISI on STN
TI Expression of hirudin fusion proteins in mammalian cells: a strategy for prevention of intravascular thrombosis;
recombinant hirudin, CD4, **P-selectin** fusion protein expression in host cell, used in thrombosis gene therapy
SO Circulation; (1998) 98, 24, 2744-52
CODEN: CIRCAZ ISSN: 0009-7322
AU Riesbeck K; Chen D; Kemball-Cook G; McVey J H; George A J T; Tuddenham E G D; Dorling A; *Lechler R I
AN 1999-05489 BIOTECHDS

L85 ANSWER 5 OF 120 MEDLINE on STN DUPLICATE 1
TI Effects of a **metalloproteinase** that truncates **P-selectin** glycoprotein ligand on neutrophil-induced cardiac dysfunction in ischemia/reperfusion.
SO Journal of molecular and cellular cardiology, (1998 Dec) 30 (12) 2561-6.
Journal code: 0262322. ISSN: 0022-2828.
AU Lefer A M; Campbell B; Shin Y K
AN 1999144339 MEDLINE

L85 ANSWER 6 OF 120 MEDLINE on STN
TI Quinine-dependent antibodies bind a restricted set of epitopes on the glycoprotein Ib-IX complex: characterization of the epitopes.
SO Blood, (1998 Oct 1) 92 (7) 2366-73.
Journal code: 7603509. ISSN: 0006-4971.
AU Burgess J K; Lopez J A; Berndt M C; Dawes I; Chesterman C N; Chong B H
AN 1998421381 MEDLINE

L85 ANSWER 7 OF 120 MEDLINE on STN
TI Effects of 0.2 ppm ozone on biomarkers of inflammation in bronchoalveolar lavage fluid and bronchial mucosa of healthy subjects.
SO European respiratory journal : official journal of the European Society for Clinical Respiratory Physiology, (1998 Jun) 11 (6) 1294-300.
Journal code: 8803460. ISSN: 0903-1936.
AU Krishna M T; Madden J; Teran L M; Biscione G L; Lau L C; Withers N J; Sandstrom T; Mudway I; Kelly F J; Walls A; Frew A J; Holgate S T
AN 1998319674 MEDLINE

L85 ANSWER 8 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Isolation and partial amino acid sequence of a novel **metalloprotease** from the **venom** of the colubrid snake Hydrodynastes gigas (false water **cobra**).
SO Toxicon, (Sept., 1998) Vol. 36, No. 9, pp. 1250. print.
Meeting Info.: 12th World Congress on Animal, Plant and Microbial Toxins. Cuernavaca, Mexico, USA. September 21-26, 1997.
CODEN: TOXIA6. ISSN: 0041-0101.
AU Mackessy, Stephen P. [Reprint author]
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L85 ANSWER 9 OF 120 MEDLINE on STN DUPLICATE 2
TI Aprotinin reduces the expression of **p-selectin** on the surface of platelet and leukocyte-platelet conjugates.
SO Artificial organs, (1998 Dec) 22 (12) 1018-22.
Journal code: 7802778. ISSN: 0160-564X.
AU Inui K; Shimazaki Y; Watanabe T; Kuraoka S; Uesho K; Uchida T; Shiono S
AN 1999091321 MEDLINE

L85 ANSWER 10 OF 120 HCAPLUS COPYRIGHT 2004 ACS on STN
TI The composition of **Naja naja** venom samples from three districts of West Bengal, India
SO Comparative Biochemistry and Physiology, Part A: Molecular & Integrative Physiology (1998), 119A(2), 621-627

CODEN: CBPAB5; ISSN: 0300-9629
AU Mukherjee, A. K.; Maity, C. R.
AN 1998:94023 HCAPLUS
DN 128:189384

L85 ANSWER 11 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Evaluation of the anticoagulant effects of a highly specific snake venom metalloproteinase.
SO Blood, (Nov. 15, 1998) Vol. 92, No. 10 SUPPL. 1 PART 1-2, pp. 552A. print.
Meeting Info.: 40th Annual Meeting of the American Society of Hematology. Miami Beach, Florida, USA. December 4-8, 1998. The American Society of Heamatology.
CODEN: BLOOAW. ISSN: 0006-4971.
AU Kumar, A.; Patel, H.; Rajewski, J.; Parmar, P.; Bond, M.; Shaw, G.; Sako, D.; Keith, J. C., Jr.; Schaub, R. G.
AN 1999:120062 BIOSIS

L85 ANSWER 12 OF 120 MEDLINE on STN DUPLICATE 3
TI Purification and characterization of kaouthiagin, a von Willebrand factor-binding and -cleaving **metalloproteinase** from Naha kaouthia **cobra venom.**
SO Thrombosis and haemostasis, (1998 Sep) 80 (3) 499-505.
Journal code: 7608063. ISSN: 0340-6245.
AU Hamako J; Matsui T; Nishida S; Nomura S; Fujimura Y; Ito M; Ozeki Y; Titani K
AN 1998430434 MEDLINE

L85 ANSWER 13 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI cDNA cloning and expression of cobrin, the C3-cleaving **metalloprotease** from **Cobra venom.**
SO Molecular Immunology, (April-May, 1998) Vol. 35, No. 6-7, pp. 408. print.
Meeting Info.: XVII International Complement Workshop. Rhodes, Greece. October 11-16, 1998.
CODEN: MOIMD5. ISSN: 0161-5890.
AU Bambai, Bijam; Teppke, Manfred; Bredehorst, Reinhard; Vogel, Carl-Wilhelm
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L85 ANSWER 14 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI The molecular and cellular biology of pancreatic cancer.
SO Critical Reviews in Eukaryotic Gene Expression, (1998) Vol. 8, No. 3-4, pp. 377-393. print.
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AN 1999:17392 BIOSIS

L85 ANSWER 15 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
TI cDNA cloning and expression of cobrin, the C3-cleaving **metalloprotease** from **cobra venom**
SO MOLECULAR IMMUNOLOGY, (APR-MAY 1998) Vol. 35, No. 6-7, Sp. iss. SI, pp. 311-311.
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ISSN: 0161-5890.
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AN 1998:745708 SCISEARCH

L85 ANSWER 16 OF 120 MEDLINE on STN DUPLICATE 4
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L85 ANSWER 17 OF 120 MEDLINE on STN DUPLICATE 5
TI The neutrophil and preeclampsia.
SO Seminars in reproductive endocrinology, (1998) 16 (1) 57-64. Ref: 98
Journal code: 8308354. ISSN: 0734-8630.
AU Clark P; Boswell F; Greer I A
AN 1998318677 MEDLINE

L85 ANSWER 18 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI **Mocarhagin**, a **cobra venom protease**
, and therapeutic uses thereof.
SO Official Gazette of the United States Patent and Trademark Office Patents, (Aug. 19, 1997) Vol. 1201, No. 3, pp. 2175. print.
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AN 2002:82166 BIOSIS

L85 ANSWER 19 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
TI Factor Xa as an interface between coagulation and inflammation - Molecular mimicry of factor Xa association with effector cell **protease** receptor-1 induces acute inflammation in vivo
SO JOURNAL OF CLINICAL INVESTIGATION, (15 MAY 1997) Vol. 99, No. 10, pp. 2446-2451.
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L85 ANSWER 20 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
TI Kaouthiagin, a **metalloproteinase** purified from **Naja** kaouthia **cobra venom**, specifically binds to and cleaves von Willebrand factor.
SO BLOOD, (15 NOV 1997) Vol. 90, No. 10, Part 1, Supp. [1], pp. 2071-2071.
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ISSN: 0006-4971.
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AN 97:879006 SCISEARCH

L85 ANSWER 21 OF 120 MEDLINE on STN DUPLICATE 6
TI A tissue plasminogen activator/**P-selectin** fusion protein is an effective thrombolytic agent.
SO Circulation, (1997 Feb 4) 95 (3) 715-22.
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L85 ANSWER 22 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
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SO Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 466A. print.
Meeting Info.: 39th Annual Meeting of the American Society of Hematology. San Diego, California, USA. December 5-9, 1997. The American Society of Hematology.
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TI Postangioplasty restenosis: platelet activation and the coagulation-fibrinolysis system as possible factors in the pathogenesis of restenosis.
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Journal code: 0370465. ISSN: 0002-8703.
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L85 ANSWER 24 OF 120 MEDLINE on STN DUPLICATE 7
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SO Current opinion in lipidology, (1997 Oct) 8 (5) 320-8. Ref: 89
Journal code: 9010000. ISSN: 0957-9672.
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L85 ANSWER 25 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
TI Tetanus toxin inhibits activation-dependent **P-selectin** surface expression in permeabilized platelets.
SO Blood, (Nov. 15, 1997) Vol. 90, No. 10 SUPPL. 1 PART 1, pp. 282A. print.
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L85 ANSWER 26 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
TI Endothelial cell injury in cardiovascular surgery: The systemic inflammatory response
SO ANNALS OF THORACIC SURGERY, (JAN 1997) Vol. 63, No. 1, pp. 277-284.
Publisher: ELSEVIER SCIENCE INC, 655 AVENUE OF THE AMERICAS, NEW YORK, NY 10010.
ISSN: 0003-4975.
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L85 ANSWER 27 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
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ISSN: 0167-6865.
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AN 97:827869 SCISEARCH

L85 ANSWER 28 OF 120 LIFESCI COPYRIGHT 2004 CSA on STN
TI Role of macrophages in vascular tissue remodelling
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ISSN: 0966-3274.
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L85 ANSWER 29 OF 120 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
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L85 ANSWER 30 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
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L85 ANSWER 31 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
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L85 ANSWER 32 OF 120 MEDLINE on STN DUPLICATE 8
TI **Mocarhagin**, a novel **cobra venom metalloproteinase**, cleaves the platelet von Willebrand factor receptor glycoprotein Ibalpha. Identification of the sulfated tyrosine/anionic sequence Tyr-276-Glu-282 of glycoprotein Ibalpha as a binding site for von Willebrand factor and alpha-thrombin.
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AN 96267086 MEDLINE

L85 ANSWER 33 OF 120 MEDLINE on STN DUPLICATE 9
TI Generation of a new gamma delta T cell-specific monoclonal antibody (GD3.5). Biochemical comparisons of GD3.5 antigen with the previously described Workshop Cluster 1 (WC1) family.
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L85 ANSWER 34 OF 120 MEDLINE on STN DUPLICATE 10
TI Effects of E-selectin and **P-selectin** blockade on neutrophil sequestration in tissues and neutrophil oxidative burst in burned rats.
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AN 96322880 MEDLINE

L85 ANSWER 35 OF 120 MEDLINE on STN DUPLICATE 11
TI Characterization of **mocarhagin**, a **cobra venom metalloproteinase** from **Naja** mocambique mocambique, and related proteins from other Elapidae venoms.
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L85 ANSWER 36 OF 120 MEDLINE on STN DUPLICATE 12
TI Interactions of human alpha/beta and gamma/delta T lymphocyte subsets in shear flow with E-selectin and **P-selectin.**
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L85 ANSWER 37 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
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L85 ANSWER 38 OF 120 MEDLINE on STN
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L85 ANSWER 39 OF 120 MEDLINE on STN DUPLICATE 13
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AN 97051972 MEDLINE

L85 ANSWER 40 OF 120 MEDLINE on STN
TI Plasma **P selectin** (GMP-140) and glycocalicin are elevated in preeclampsia and eclampsia: their significances.
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L85 ANSWER 41 OF 120 MEDLINE on STN DUPLICATE 14
TI Flow cytometric evaluation of the effect of various thrombin inhibitors on platelet activation in whole blood.
SO Thrombosis research, (1996 May 1) 82 (3) 257-63. Journal code: 0326377. ISSN: 0049-3848.
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AN 96311055 MEDLINE

L85 ANSWER 42 OF 120 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
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SO GLYCOBIOLOGY, (MAR 1996) Vol. 6, No. 2, pp. 191-208. ISSN: 0959-6658.
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L85 ANSWER 43 OF 120 MEDLINE on STN DUPLICATE 15
TI A novel **cobra venom metalloproteinase**, **mocarhagin**, cleaves a 10-amino acid peptide from the mature N terminus of **P-selectin** glycoprotein ligand receptor, **PSGL**-1, and abolishes **P-selectin** binding.
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L85 ANSWER 44 OF 120 MEDLINE on STN DUPLICATE 16
TI Primitive human hematopoietic progenitors adhere to **P-selectin** (CD62P).
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Journal code: 7603509. ISSN: 0006-4971.
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AN 95299131 MEDLINE

L85 ANSWER 45 OF 120 MEDLINE on STN DUPLICATE 17
TI Specific sensitivity of CD43 to neutrophil elastase.
SO Blood, (1995 Sep 15) 86 (6) 2395-402.
Journal code: 7603509. ISSN: 0006-4971.
AU Remold-O'Donnell E; Parent D
AN 95392000 MEDLINE

L85 ANSWER 46 OF 120 HCAPLUS COPYRIGHT 2004 ACS on STN
TI Functional analysis of **P-selectin** mAb of the selectin panel
SO Leucocyte Typing V: White Cell Differentiation Antigens, Proceedings of the International Workshop and Conference, 5th, Boston, Nov. 3-7, 1993 (1995), Meeting Date 1993, Volume 2, 1512-1514. Editor(s): Schlossman, Stuart F. Publisher: Oxford University Press, Oxford, UK.
CODEN: 63WDAC
AU De Bruijne-Admiraal, Lucia G.; Von Dem Borne, Albert E. G. Km.
AN 1997:47476 HCAPLUS
DN 126:87602

L85 ANSWER 47 OF 120 MEDLINE on STN DUPLICATE 18
TI Isolation and properties of a blood coagulation factor X activator from the venom of king **cobra** (Ophiophagus hannah).
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Journal code: 1307333. ISSN: 0041-0101.
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AN 96151321 MEDLINE

L85 ANSWER 48 OF 120 MEDLINE on STN
TI Cross-reactivity of human molecular markers for detection of prethrombotic states in various animal species.
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L85 ANSWER 49 OF 120 MEDLINE on STN DUPLICATE 19
TI Influence of temperature on neutrophil trafficking during clinical cardiopulmonary bypass.
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Journal code: 0147763. ISSN: 0009-7322.
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AN 96069224 MEDLINE

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